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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,033	05/11/2001	Pierre Chambon	065691-0222	5081

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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,033	CHAMBON ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-19,21-33,35-49,51-61 and 66-86* is/are pending in the application.

4a) Of the above claim(s) *9,13,15-18,21,22,24-32,35-49,51 and 53-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,10-12,14,19,23,33,52 and 66-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Claims 1, 4-19, 21-33, 35-49, 51-61, 66-86 are pending in the application.

Claims 9, 13, 15-18, 21, 22, 24-32, 35-49, 51, 53-61 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1, 4-8, 10-12, 14, 19, 23, 33, 52, 66-86 are currently under examination.

This Office Action is in response to the Amendment filed on 7/1/05.

Response to Amendment

The rejection of claims 1, 4-8, 10-12, 14, 19, 23, 33 and 52 under 35 U.S.C. 103 (a) has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1, 4-8, 10-12, 14, 19, 23, 33, 52, 65 and 66 under 35 U.S.C. 112 1st paragraph is maintained for reasons set forth of the record mailed on 3/25/05 and further discussed below. Newly added claims 67-86 are rejected for same reasons.

Claims 69-77, 82-86 are rejected under 35 U.S.C. 112, second paragraph for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, 10-12, 14, 19, 23, 33, 50, 52, 65-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising in its genome a first transgene comprising Cre recombinase fused to a mutated ER, wherein such

mutation result in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene exhibits a specific transgene dependent phenotype, for example, increased glucose level and decreased triglyceride level when both copies of RXRα alleles are disrupted, as compared to mouse having RXRα expression, does not reasonably provide enablement for any transgenic mouse comprising a cell comprising claimed transgenes. Further, the specification does not enable any transgenic mouse without any phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to this rejection, Applicants argue that the claimed invention is conditional recombination of DNA sequences in a mouse. Applicants further submit eight references to support the enablement of said invention. Applicants assert that a phenotype is not always a visible, observable characteristic, wherein mouse without a visible phenotype is also useful for studying/identifying the particular function of a gene. Applicants thus conclude that the claimed invention is enabled by the instant specification.

The above arguments have been fully considered but deemed unpersuasive. As discussed in the previous office action, the claimed invention does not recite any phenotype (either primary or secondary). The claims do not recite any visible observable or detectable characteristic of the claimed mice other than their genotype. Knocking out/ablation of a gene itself is not considered as a phenotype because it is a description of the genetic structure. The phenotype of the transgenic mouse is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356

(CCPA 1976). The specification discloses using the mouse as disease model or screening drugs, such embodiments are not enabled if the mouse does not have a detectable phenotype. In response to Applicant's argument with regard to use a transgenic mouse without phenotype to study the function of a gene, Applicants are reminded that the utility of the mouse need to be credible, substantial and specific such that the claimed mouse has a real world use. Studying gene function using a transgenic mouse without a phenotype is not a patentable use because it is not substantial. The eight references are fully considered, however, it does not provide sufficient support to the claimed scope. When considering post-filing reference, it only enables the invention to the scope wherein it follows the teaching of the specification and result in a specific conditional knockout mouse. Applicants are also reminded that the specification only discloses a transgenic mouse comprising a transgene encoding the claimed fusion protein, but not mice comprising the fusion protein target cells only. Therefore, for reasons discussed in the previous office action and above, this rejection is maintained.

Note, if the claim is directed to a specific conditional knockout mouse (for example, aP2-Cre-ER T2/RXRα L2/L2) with phenotype recited in the claims, it is allowable.

Newly added claims 69-86 are also rejected because it is enabled to the scope of using a transgenic mouse comprising in its genome a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising Cre recognition sites flanking the endogenous gene of interest. The claims are not enabled for any transgenic mouse wherein only targeted cell comprises the transgene or the fusion protein. Further, claim 72 is not enabled for step d) wherein the fusion protein is injected directly into the target cells.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a method of producing transgenic mouse by modifying a somatic cell by homologous recombination, and subsequently generation of transgenic mouse by nuclear transfer. At the time of filing, homologous recombination is somatic cells is considered unpredictable, especially in un-transformed cells. The frequency of homologous recombination events in normal differentiated somatic cells is very low compare to embryonic stem cells, wherein mammalian cells repair double stranded breaks very efficiently by end joining. Further, nuclear transfer is also limited to specific types of somatic cells. Since the specification does not teach specifically what types of specific somatic cells are used in the claimed method, or methods to overcome the art recognized difficulty, one skilled in the art would have to engage in undue experimentation to practice the method as claimed. Therefore, the claimed invention is not enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-77, 82-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 69-77, 82-86, the recitation of "transgenic mouse, wherein target cells of said transgenic mouse comprises at least: a Cre fusion protein" renders the claim indefinite because it is unclear whether the transgenic mouse comprises a transgene that encodes said protein or the target cells express said protein. If it is the later case, then it is unclear whether the transgenic mouse comprises any transgene or the transgene that expresses said protein. As such, the metes and bounds of the claim cannot be established.

Regarding claims 70-73, the recitation of "a method of producing a transgenic mouse according to step a) of claim 69, comprising the following step" renders the claims indefinite because step a) of claim 69 is "obtaining a transgenic mouse..." It is unclear whether the claims are drawn to a method of obtaining said mouse or the method of claim 69 which further comprises additional steps recited in claims 70-73.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims 9, 13, 15-18, 21, 22, 24-32, 35-49, 51, 53-61, drawn to an invention nonelected with traverse in the Response filed on 10/9/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER